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ORIGINAL ARTICLE

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Significance of a new fluorodeoxyglucose-positive lesion on restaging positron emission tomography/computed tomography after induction therapy for non-small-cell lung cancer[†]

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Abstract

OBJECTIVES: Restaging of patients with locally advanced non-small-cell lung cancer (NSCLC) is of paramount importance, since only patients with down-staging after induction therapy will benefit from surgery. In this study, we assessed the aetiology of new ^{18}fluoro-2-deoxy-D-glucose (FDG)-positive focal abnormalities on restaging positron emission tomography/computed tomography (PET/CT) in patients with a good response after induction chemotherapy in the primary tumour and lymph nodes.

METHODS: Between 2004 and 2008, 31 patients with histological proven stage III NSCLC had a PET/CT prior and after induction chemotherapy. Their medical charts were retrospectively reviewed.

RESULTS: Restaging PET/CT revealed a new FDG-positive lesion in 6 of 31 (20%) patients. The initial clinical stage of the disease was IIIA N2 in four and IIIB T4 in two patients. The maximal standard uptake value in the primary tumour ($P = 0.043$) and in the initially involved mediastinal nodes ($P = 0.068$) decreased after induction treatment in all patients. The new PET/CT findings were located in an ipsilateral cervical lymph node in two patients, a contralateral mediastinal in one patient and an ipsilateral mammary internal lymph node in one patient. Two other patients had a lesion on the contralateral lung. Malignant lymph node infiltrations were excluded following fine-needle puncture, intraoperative biopsy or follow-up PET/CT. Contralateral pulmonary lesions were diagnosed as benign following mini thoracotomy and pulmonary wedge resection.

CONCLUSIONS: New solitary FDG-positive lesions on restaging PET/CT after induction chemotherapy for NSCLC are not rare in good responders to chemotherapy. In our experience, all these lesions were not associated with malignancy.

Keywords: Lung • Cancer • Positron emission tomography • Imaging • Adjuvant/neoadjuvant therapy

INTRODUCTION

Patients with clinical stage III-N2 or -T4 non-small-cell lung cancer (NSCLC) have a poor prognosis when treated with surgery alone. In order to improve outcome, the concept of preoperative induction therapy was introduced. It has been shown that induction chemotherapy (or radiochemotherapy) combined with surgery is effective in selected subgroups of patients such as patients with IIIA-N2 disease [1, 2]. Recent studies suggested that mediastinal down-staging and complete resection after induction are significant factors for better outcome in cases of stage IIIA or IIIB disease. But several reports have also described an increased perioperative morbidity and mortality for surgical resection following induction therapy compared with resection without induction treatment [3]. Therefore, restaging after induction therapy plays a central role in selecting candidates for resection.

^{18}Fluoro-2-deoxy-D-glucose positron-emission tomography with integrated computed tomography (FDG-PET/CT) has become widely adopted as a major tool for the staging of NSCLC and has been increasingly incorporated into the routine work-up for restaging after induction therapy. However, due to poor sensitivity of 50–60%, PET scan for mediastinal restaging is not as accurate as prior to induction [4–8].

In this study, we assessed the significance of new solitary FDG-positive lesions on restaging PET/CT located in lymph

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Table 1: Patient and tumour characteristics

Patient	Gender	Age (years)	Histology	cStage	Location of the primary
1	w	44	Adeno	T1N2	Left upper lobe
2	m	61	Large cell	T2N2	Left upper lobe
3	m	58	Squamous cell	T2N2	Middle lobe
4	w	51	Adeno	T2N2	Right upper lobe
5	m	62	Large cell	T4N0	Left upper lobe
6	m	60	Squamous cell	T4N1	Right lower lobe

nodes or in the contralateral lung in patients who showed a good radiological response in the primary tumour and in the mediastinal nodes after induction therapy.

MATERIALS AND METHODS

Between January 2004 and March 2008, an integrated whole-body PET/CT was carried out on a consecutive series of 603 patients with potentially operable NSCLC. Conventional staging by means of a history, physical findings, blood test, bronchoscopy and contrast medium-enhanced CT scan of the chest and upper abdomen was carried out in all patients. A hundred and forty-five (24%) of these patients with clinical stage III disease underwent induction chemotherapy or radiochemotherapy. Restaging was carried out by use of CT scan. Patients without evidence of disease progression after restaging underwent surgery. Anatomical resection of the primary tumour combined with a mediastinal lymph node dissection was carried out whenever possible according to the lung function test after induction and to the intraoperative findings.

In 31 patients, additional restaging PET/CT was carried out 4 weeks after induction therapy. Stage IIIA was observed in 26 patients and stage IIIB in 5 patients. Stage IIIA included T1N2, T2N2, T3N1 and T3N2 in 2, 16, 1 and 7 patients, respectively, whereas stage IIIB included T4N0, T4N1 and T4N2 in 1, 2 and 2 patients. In patients with stage IIIA N2, suspected tumour involvement of the mediastinal lymph nodes on PET/CT had been confirmed histologically by use of videomediastinoscopy before induction treatment. In patients with clinical stage IIIB T4, PET/CT demonstrated several positive satellite nodes in the same lobe in three patients and suspicion of infiltration of the superior vena cava in two patients. All patients underwent induction chemotherapy alone, consisting of a combination of platinum (100 mg/m^2) and gemcitabine (1000 mg/m^2) in 13 patients and of platinum and taxotere (85 mg/m^2) in 18 patients. Stable disease, partial and total remissions occurred in 9 (29%), 21 (68%) and 1 (3%) patients. The data of the pre- and post-induction PET/CT examinations were reviewed in these 31 patients. Patient informed consent was obtained prior to surgery for performing this analysis.

RESULTS

Restaging PET/CT revealed a new solitary focal abnormality in 6 of 31 (20%) patients after induction therapy. Characteristics of these six patients, histology, clinical stage of the disease and location of the primary are shown in Table 1. Induction

Table 2: Values of SUVmax before and after induction treatment in the primary lung tumour and in the mediastinal lymph nodes

Patient	Primary tumour, SUVmax		Mediastinal lymph nodes, SUVmax	
	Pre-induction	Post-induction	Pre-induction	Post-induction
1	7.3	2.7	6.6	0.1
2	10.7	4.4	8.4	3.8
3	7.9	4.8	4.3	2.8
4	16.8	6.4	16.7	3.2
5	10.4	1.2		
6	9.6	5.7		
	$P = 0.043$[a]		$P = 0.068$[a]	

*[a]Non-parametric Wilcoxon test.

Table 3: Characteristics of the new focal abnormalities revealed on restaging PET/CT after induction chemotherapy

Patient	New focal post-induction abnormality (SUVmax)	Diagnostic procedure	Diagnosis
1	Ipsilateral cervical LN (5.4)	FNP	Reactive LN
2	Ipsilateral cervical LN (7.2)	FNP	Reactive LN
3	Contralateral LN ATS 2L (5.7)	Follow-up PET/CT	Reactive LN
4	Contralateral LUL (3.8)	Wedge resection LUL	Pneumonia
5	Ipsilateral mammary internal LN (3.1)	Intraoperative resection	Reactive LN
6	Contralateral LUL (9.6)	Wedge resection LUL	Aspergilloma

LN, lymph node; LUL, left upper lobe; FNP, fine-needle puncture.

treatment could be completed in all patients. Transient neutropenia and gastroenteritis were observed in one patient.

In all patients, restaging PET/CT showed an important decrease of the FDG uptake in the primary tumour as well as in the mediastinal lymph nodes which were strongly PET positive before induction treatment. Despite the small number of patients, the decrease of maximal standard uptake value (SUVmax) was significant for the primary tumour (non-parametric Wilcoxon test). Table 2 gives the values of SUVmax in the primary and in the lymph nodes before and after induction therapy. This radiological response to chemotherapy could be confirmed histopathologically by the presence of necrosis in the operative specimen. Median necrosis values for the primary tumour and for the lymph nodes were 45 and 20%, respectively.

The six new focal abnormalities revealed at restaging PET/CT after induction chemotherapy were located in an ipsilateral cervical lymph node in two patients, in the contralateral upper lobe in two patients and in a contralateral paratracheal lymph node and an ipsilateral mammary internal lymph node in one patient, respectively (Table 3). These new PET-positive lesions showed a high SUVmax, with a mean value of 5.8 ± 2.2. Diagnostic procedures were carried out in five of six patients. Two patients

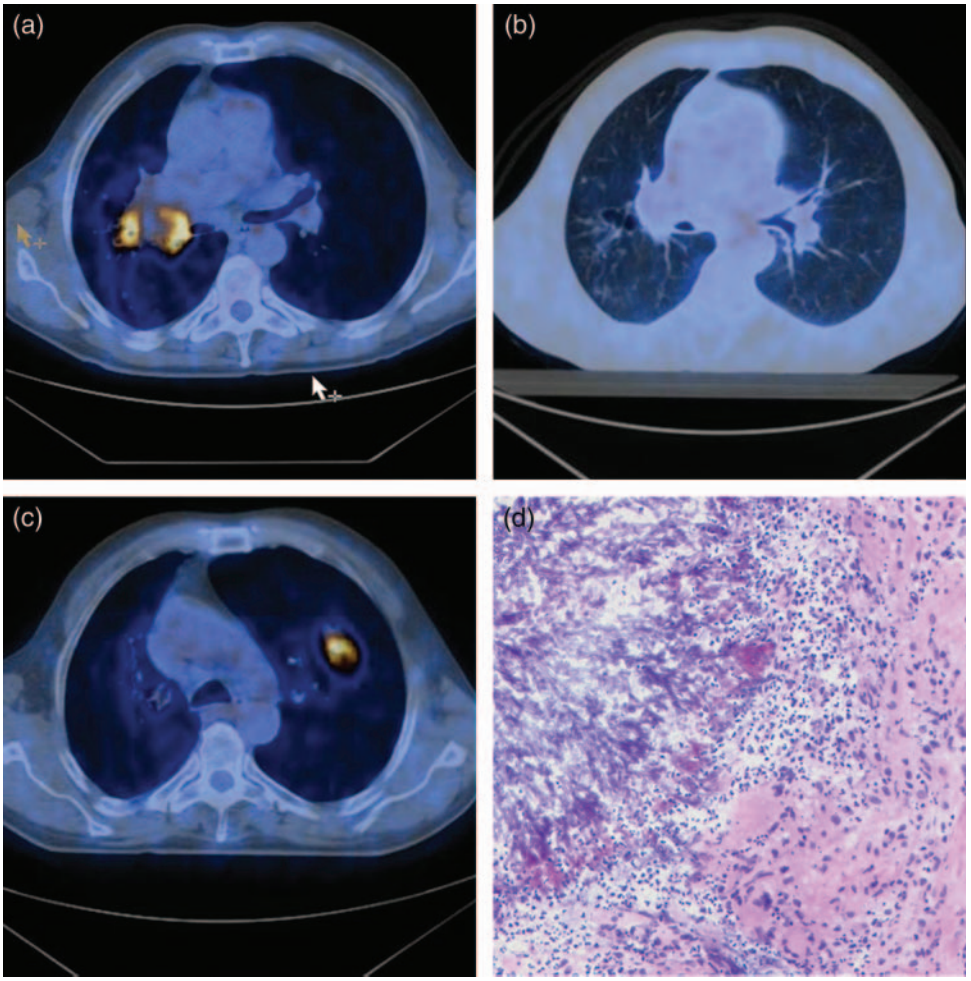

Figure 1: A 60-year-old man with a central squamous cell carcinoma coming from the right lower lobe. (a) Axial PET/CT scan showed the high FDG primary tumour before induction therapy. (b) Restaging axial PET/CT scan demonstrated the partial response of the primary tumour after induction therapy. (c) Restaging axial PET/CT scan revealed the new solitary PET-positive lesion in the contralateral upper lobe. (d) Histopathology of the lung parenchyma FDG-positive lesion revealed an aspergilloma.

underwent a mini thoracotomy followed by a wedge resection of the contralateral left upper lobe without postoperative complication. Histopathological diagnosis revealed aspergilloma in the first (Fig. 1) and pneumonia in the second patient. Both patients could undergo complete lung resection consisting of right pneumonectomy and right upper lobectomy.

Two patients had preoperative fine-needle punctures of cervical lymph node (Fig. 2) and one had intraoperative resection of a mammary internal lymph node. Histological/cytological examination revealed benign reactive lymph nodes in all patients. In the last patient, follow-up PET/CT at 1 month showed no focal abnormality anymore and could exclude therefore tumour involvement of the contralateral mediastinal lymph node.

DISCUSSION

In the 1990s, induction therapy, including preoperative radiochemotherapy or chemotherapy alone, has been increasingly used for locally advanced stage III NSCLC in order to downstage tumours and render them completely resectable [9, 10]. Several studies have shown a strong survival benefit in patients with stage IIIA-N2 disease who have been down-staged by induction therapy in comparison with patients with residual N2 disease [1, 2]. It has also been shown that surgery can be carried out in a curative intent in highly selected patients with stage IIIB-T4 disease within a multimodality therapy concept. The most important prognostic factors are complete resection and the absence of mediastinal lymph node involvement. As a consequence, accurate restaging after induction therapy is of paramount importance in these subgroups of patients. The difficulty is to assess the pathological response after induction treatment. In many centres restaging CT alone is carried out, despite its low accuracy in restaging the mediastinum. Its sensitivity varied from 41 to 59% and its specificity from 75 to 62% with an accuracy of 58 and 60% [11, 12]. More invasive techniques such as endoesophageal ultrasound-guided fine-needle aspiration (EUS-FNA), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy offer the advantage of providing cytological/histological evidence of response after induction treatment. Until recently, these endoscopic techniques have been studied fully in restaging N2 patients. In a pioneer study, Annema and collaborators assessed the accuracy of EUS-FNA for restaging the mediastinum after induction chemotherapy in 19 patients with proven N2 disease. The positive predictive value, negative predictive value, sensitivity, specificity and

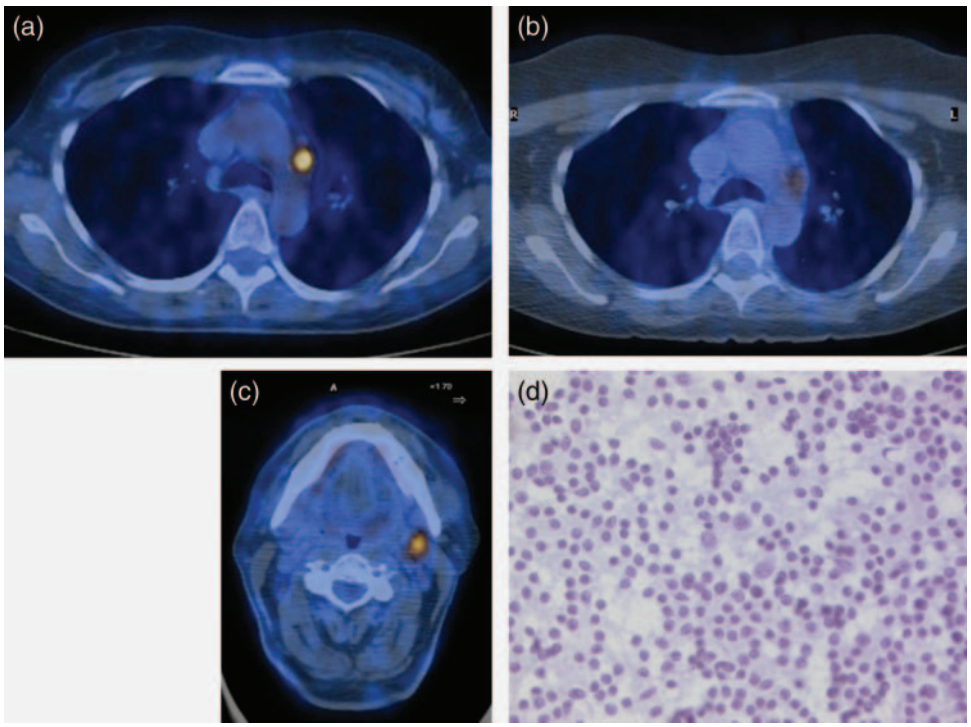

Figure 2: A 61-year-old man with a large-cell carcinoma of the left upper lobe and ipsilateral mediastinal lymph node invasion. (a) Axial PET/CT scan showed the high FDG activity within the ipsilateral mediastinal lymph node. (b) Restaging axial PET/CT scan demonstrated the partial response of the mediastinal lymph node after induction therapy. (c) Restaging axial PET/CT scan revealed the new solitary PET-positive lesion in the cervical lymph node. (d) Cytology after fine-needle puncture revealed a reactive lymph node.

diagnostic accuracy of EUS-FNA in this small group of patients were 100, 67, 75, 100 and 83%, respectively [13]. More recently, Herth *et al*. published the results of a large trial evaluating EBUS-TBNA in restaging the mediastinum after induction chemotherapy in 124 patients with NSCLC. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 76, 100, 100, 20 and 77%, respectively. Therefore, the authors recommended the need to confirm EBUS-FNA tumour-negative mediastinal nodes by surgical staging before thoracotomy [14]. Repeated mediastinoscopy, although technically more difficult than the first procedure due to adhesions and mediastinal fibrosis, is technically feasible in experienced hands [15]. In different series, its sensitivity after induction therapy for mediastinoscopy proven N2 disease was reported from 70 to 78% except in one prospective study with a reported sensitivity to detect mediastinal disease of 29% [11, 12, 16–18]. This low sensitivity was largely explained by the fact that biopsy of the subcarinal nodes was not adequately carried out in two of three of patients.

In our study, we used whole-body integrated PET/CT for restaging in 31 patients. Accuracy of PET/CT was assessed in different settings related to induction protocol (chemotherapy or chemoradiotherapy), timing of imaging (from 1 to 10 weeks post-induction) and interpretation of imaging (visual or standardized uptake value). Its sensitivity and specificity in three different studies were 77 and 92%, 73 and 89% and 62 and 88%, respectively [12, 19, 20]. Although accuracy of PET/CT in restaging is lower than for staging untreated patients, it enables the direct correlation of FDG-accumulating lesions with morphologic structures throughout the body. It has also been shown that the comparison of SUVmax values before and after induction treatment allowed prediction of histopathological response in the primary tumour and in the mediastinal lymph nodes, therefore carrying an important prognostic value [19, 21]. In the present study, restaging PET/CT showed a marked response in primary tumour ($P = 0.043$) and in mediastinal nodes ($P = 0.068$) after induction chemotherapy for all patients, indicating a favourable outcome. Surprisingly, restaging PET/CT revealed new solitary high FDG-positive lesions in cervical or contralateral mediastinal lymph nodes as well as in the contralateral lung. There was a discrepancy since FDG uptake had strongly decreased in the primary and in the involved lymph nodes. The clinical significance of these new findings was unclear. Was it a metastasis or a second tumour resistant to the induction treatment? Further management of the patient would strongly differ according to the neoplastic or inflammatory nature for the lesions. Cytological/histopathological diagnosis was then mandatory. We carried out preoperative fine-needle punctures for cervical lymph nodes as well as an intraoperative resection of the mammary interna lymph node. These procedures revealed inflammatory reactive lymph nodes. The same diagnosis could be deducted in a mediastinal contralateral lymph node from the disappearance of the lesion's high FDG-uptake on follow-up PET/CT. Regarding FDG-positive lesions in the contralateral lung, histopathological examination revealed an aspergilloma and pneumonia.

New solitary high FDG accumulation in lymph node or contralateral parenchymal lung on restaging PET/CT after induction chemotherapy in good responders with locally advanced NSCLC were not rare (6 of 31 or 20%). In our experience, these FDG-positive lesions did not imply progression of the disease since they were diagnosed as benign lesions in all six patients. Therefore, extensive diagnostic procedures for these lesions could be avoided in the future if larger studies confirm our findings.

Conflict of interest: none declared.

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